Attorney Docket No. ARC 2914 R1

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14/Appeal Brief (3)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant(s)	: Berry et al.	)
Serial No.	: 09/497,422	) Art Unit: 1615
Filed	: February 3, 2000	) Examiner: J. M. Spear
For	: Stable Non-Aqueous Single Phase Viscous Vehicles and Formulations Utilizing Such Vehicles	) (Primary Examiner)))

Bef 7-3-01

Assistant Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

BRIEF FOR APPLICANT PURSUANT TO 37 C.F.R. § 1.192

I. INTRODUCTION

This is an appeal to the Honorable Board of Appeals and Interferences from the Primary Examiner's Art Unit 1615, final rejection of December 28, 2000 (Paper No. 9). An Amendment after Final Rejection was filed on March 28, 2001. A Notice of Appeal was filed on March 28, 2001. An Advisory Action was issued April 27, 2001 which did not enter the amended claims. This is an appeal under 37 C.F.R. §1.191 of the final rejection set forth in the Official Action dated December 28, 2000. This Appeal Brief is in compliance with the format stated in

37 C.F.R. §1.192 and the two additional copies of the Brief and the required Official Fee under 37 C.F.R. §1.17(c) have also been provided herewith.

II. REAL PARTY IN INTEREST

The real party in interest is ALZA Corporation of Mountain View, California, to which all of the inventions, Stephen A. Berry, Pamela J. Fereira, Houdin Dehnad, and Anna Muchnik, have assigned the invention.

III. RELATED APPEALS AND INTERFERENCES

Based on present knowledge there are no related appeals or interferences that will directly affect or be directly affected by or have a bearing on the decision by the Board of Patent Appeals and Interferences concerning the instant appeal.

IV. STATUS OF THE CLAIMS

Claims 1-38 are presently on appeal. Claims 1-33 and 35-38 have been rejected under 35 U.S.C.§103(a) as being obvious over a combination of one U.S. patent and one PCT publication in view of a second U.S. patent. Claim 34 has been objected to as depending from a rejected claim. For this appeal Applicant has treated claim 34 as being rejected. A copy of the claims on appeal is provided in Appendix A.

V. STATUS OF AMENDMENTS

In response to the Final Official Action dated December 28, 2000, an Amendment after Final was filed on March 28, 2001, canceling claim 2, amending claims 1, 3, 4, 5, 6, 7, 8, 12, 14, 15, 29, and 30, and adding claims 39, 40, 41, and 42 to address a rejection under 35 U.S.C. §103(a). The Advisory Action dated April 27, 2001, indicated that the amendment would not be entered because additional claims were proposed without canceling a corresponding number of finally rejected claims. The Advisory Action also indicated that the

amendments did not place the claims in condition for allowance and that "[t]he scope of the claims broadly read on the prior art which teaches the generic concept of two carrier vehicle/system." A copy of the claims as submitted in the Amendment after Final is provided in Appendix B.

VI. SUMMARY OF THE PRESENTLY CLAIMED INVENTION

A. Background

The stability and activity of large molecules presented to a patient for the prevention, diagnosis, and/or treatment of disease has been of substantial concern in the health care profession. Proteins are naturally active in aqueous solutions. However, proteins are only marginally stable in aqueous solutions, being prone to aggregation and precipitation. Thus pharmaceuticals containing large molecules such as proteins often have short shelf-lives under ambient conditions or require refrigeration.

Because proteins can easily degrade, the standard method for delivering such compounds has been daily injections. The injection formulations are either prepared just before injection, or are kept at refrigerator temperatures

One approach to preparing stable protein formulations has been to dry them using various techniques. Dried proteins can be stored until their use is required. Just prior to use, the dried proteins are made into formulations and provided to the patient.

Another approach is to stabilize the protein before being made into a formulation. This approach includes making polymer matrices or microparticles containing the protein. When a solvent is added, the protein is protected or stabilized by the polymer matrix or microparticle.

Solution formulations of proteins/peptides in non-aqueous polar aprotic solvents have been shown to be stable at elevated temperatures for long periods of time. However, such solvent based formulations are not useable for all proteins since many proteins have low solubility in these solvents. The lower the solubility of the protein in the formulation, the more solvent would have to be

used for delivery of a specific amount of protein. Low concentration solutions may be acceptable for injections, but may not be useful for long term delivery at low flow rates.

B. The Present Invention

The presently claimed invention relates to non-aqueous single phase viscous vehicles capable of suspending and dispersing proteins at low flow rates over an extended period of time at body temperature. The non-aqueous single phase viscous vehicles are prepared by mixing at least two components consisting of solvent, surfactant and polymer wherein the two components are not of the same type. The non-aqueous single phase viscous vehicles can also be prepared by mixing at least three components consisting of solvent, surfactant and polymer. The finished vehicle is measured using differential scanning calorimetry (DSC) to determine that it is a single phase vehicle (see page 11, lines 19-22). The solvent in the vehicle is selected from the group carboxylic acid esters, polyhydric alcohols, polymers of polyhydric alcohols, fatty acids, oils, propylene carbonate, lauryl alcohol, and esters of polyhydric alcohols. The surfactant of the vehicle is selected from the group esters of polyhydric alcohols, ethoxylated castor oil, polysorbates, esters or ethers of saturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers. The polymer of the vehicle is selected from the group polyesters, pyrrolidones, esters or ethers of unsaturated alcohols, and polyethylenepolyoxyproylene block copolymers. The Viscosities of the non-aqueous single phase viscous vehicles of this invention range between about 1,000 and 10,000,000 poise (see page 11, lines 11-13). The currently preferred vehicles have a viscosity in the range of about 10,000 to 250,000 poise. Examples of the two and three component non-aqueous single phase viscous vehicles of the present invention are shown in the specification, for example see Example 1, and Table 3 on page 21 of the specification.

The presently claimed invention also relates to formulations of a beneficial agent suspended in a non-aqueous single phase viscous vehicle of the present invention. The beneficial agent formulation can be uniformly dispensed over a long term at a low flow rate.

The presently claimed invention also related to methods for preparing both the non-aqueous single phase viscous vehicles and formulations utilizing such vehicles.

In addition, the presently claimed invention also relates to methods of treatment using formulations of the present invention.

Sustained or long term or extended term delivery of drugs has many advantages. Use of implantable devices assures patient compliance. With one insertion of a device there is reduced site irritation over daily or repeated injections, fewer occupational hazards for practitioners, improved cost effectiveness through decreased costs of equipment for repeated injection, reduced hazards of waste disposal, and enhanced efficacy through controlled release as compared with depot injection.

For example, a beneficial agent may need to be delivered in measured or predetermined quantities for 3, 6, or even 12 months or longer. If a beneficial agent is to be delivered over that period of time, the formulation must be stable for that period of time. If the formulation is to be present at body temperatures for that period of time the drug formulation must be stable at elevated temperatures for 3, 6, or even 12 months or longer. If the beneficial agent is to be delivered in measured or predetermined quantities over that time period, then the beneficial agent must be uniformly suspended in the vehicle over that time period and the vehicle must remain single phase over that time period.

VII. ISSUES ON APPEAL

The issues on appeal are whether claims 1-33 and 35-38 have been properly rejected under 35 U.S.C. §13(a) over *Knepp et al* and *Roorda et al* in

view of *Nuwayser* and whether claim 34 has been properly objected to as depending from a rejected claim.

VIII. GROUPING OF CLAIMS

The claims do not all stand of fall together for the reasons that will be apparent from the following arguments.

IX. THE REJECTIONS AT ISSUE

A. The Prior Art Relied on by the Examiner

1. Knepp et al. (the '250 Publication)

Knepp et al. teaches formulations of an active agent suspended in anhydrous, aprotic, hydrophobic, non-polar vehicles with low reactivity. The vehicles listed in Knepp et al. are mineral oil, perfluorodecalin, methoxyflurane, perfluorotributylamine, and tetradecane. The '250 publication provides a general discussion of ingredients that might be added to the formulations, however the examples in Knepp et al. are all single component vehicles. Example 1 teaches perfluorodecalin, methoxyflurane, or mineral oil. Example 2 teaches perfluorodecalin or mineral oil. Example 3 teaches perfluorodecalin or methoxyflurane. Example 4 teaches perfluorodecalin. Example 5 teaches perfluorodecalin, perfluorortributylamine, or tetradecane. On page 9, lines 14-21, Knepp et al. teaches that the non-aqueous formulations of the '250 publication comprise 2 components: 1) a protein in a stabilized powder formulation of low protein hydration; and 2) an anhydrous, hydrophobic, aprotic, non-polar vehicle of low reactivity and solubility power towards protein compounds. Although Knepp et al. teaches formulations that may optionally contain stabilizers and other excipients, the vehicle listed on page 9 is a single component vehicle.

On page 12, lines 23-32, Knepp et al. teaches that the proteinaceous particles of the '250 publication may optionally include excipients such as carbohydrates, non-ionic surfactants, buffers, salts, carrier proteins,

preservatives and the like. However the proteinaceous powders of Knepp et al. do not contain polymers, nor are they encapsulated by polymeric materials (such as mixed with the active agent in Roorda et al. or Nuwayser.

Knepp et al. also teaches (page 17, lines 9-31) preparation of active agents such as proteinaceous or nucleic acid powders by adding protective agents to the active agent during the processing steps. Thus excipients in Knepp et al. are added to the active agent during processing, not to the ahydrous, hydrophobic, aprotic, non-polar vehicle prior to the addition of the active agent (see page 18, lines 9-13 of Knepp et al.)

2. Roorda et al. (the '912 Patent)

Roorda et al. teaches aqueous formulations in which an active agent is mixed with a polymeric binder (see column 3, lines 25-28). The polymeric binder is a matrix that retains the biologically active agent. Although there is a mention that the liquids can be aqueous, non-aqueous, or undiluted non-aqueous liquids (see column 3, lines 53-55), all of the examples teach aqueous formulations. Example 1 teaches bupivacaine in aqueous sodium carboxymethylcellulose. Example 2 teaches extrusion of particles similar to those of Example 1 to form pellets. Example 3 teaches pellet preparation similar to Example 2. Example 4 teaches suspension of the pellets in an aqueous sodium carboxymethylcellulose solution. Example 5 teaches an aqueous solution similar to that in Example 4. Example 6 teaches the pharmacological efficacy of minipellets of bupivacaine in aqueous sodium carboxymethylcellulose solution.

Roorda et al. teaches that a non-aqueous solution will generally contain a solute that raises the viscosity of the non-aqueous liquid such as cottonseed oil or any other type of biocompatible oil (see column 3, lines 57-60). However, no further details, nor examples are given of non-aqueous solutions. There is also no discussion of the nature of the vehicle (e.g., whether the vehicle is single phase).

In column 4, lines 1-23), Roorda et al. teaches aqueous solutions containing a viscosity-elevating solute. Examples of the solute are sugars, oligomers and polymers. A list of polymeric species is given for preferred aqueous solutions.

3. Nuwayser (the '687 Patent)

Nuwayser teaches transdermal formulations in which active agent is incorporated in polymer microparticles that are then ground and coated with a film-forming polymer. These coated microparticles are then suspended in dermatologically acceptable viscous liquid bases. In column 7, lines 14-19, Nuwayser teaches that the microparticles or microspheres suspended in the liquid base material comprise solid mixtures of the drug in a polymer. There are no sections of the '687 patent labeled as examples, however, there are figures. Figure 1 teaches coated microparticles in Vaseline as the base. Figure 2 teaches the active agent in poly-(L)-lactide microparticles in Vaseline as the base. Figure 3 teaches the active agent in polylactide (the base is not listed for this figure). There is a mention in Nuwayser that various bases can be used, and that other ingredients can be added to the formulation. However, all of the figures use one component for preparation of the coated microparticles and Vaseline as the base.

B, The Examiner's Rationale for the Rejections Based on 35 U.S.C. §103(a)

1. The Examiner's Rationale for the Obviousness Rejection Based on the '250 Publication

In the first office action the Examiner explained the rejection based on the '250 publication (Knepp et al.) by stating:

> Knepp et al. discloses a stable non-aqueous formulation comprising of suspensions of hormones, peptides, polypeptides, proteins, nucleic acids in non-aqueous, anhydrous, aprotic, hydrophobic, non-polar vehicles having low reactivity (abstract,

and y, lines 15-19). The non-aqueous delivery system of Knepp et al. is implantable, ambulatory infusible and injectable device for sustained delivery (page 6, lines 24-25). These stable formuations of Knepp et al. are flowable and as such can be shipped and stored at high temperatures or in implantable delivery devices for long term delivery of drug for 1-12 months or longer (page 6, lines 25-28). Knepp et al. teaches that the flowable formulation may optionally include sucrose, sorbitol, raffinose and dextran to reduce the effective hydration; mannitol to modify the processing characteristics of the proteins or nucleic acids; buffers to modify the pH; and non-ionic surfactants to protect the surface and solubilize the protein or nucleic acid (page 17, lines 19-30). According to Knepp et al., the powdered flowable formulation is uniformly dispersed in anhydrous, non-polar, aprotic, hydrophobic, or low-reactivity vehicle (page 7, lines 23-24) such as mineral oil (page 8, line 27), and in example 3, page 23, Knepp et al. describes the suspension of plasma protein powder to perflourodecalin or methoxyflurane vehicles.

2. The Examiner's Rationale for the Obviousness Rejection Based on the '912 Patent

In the first office action the Examiner explained the rejection based on the '912 patent (Roorda et al.) by stating:

> Roorda et al. discloses a controlled or sustained release drug delivery system (column 1, lines 5-8), and teaches a viscous controlled release liquid formulation comprising dispersing biologically active particles in high viscosity liquid or semi-liquid. Roorda et al. teaches formulating the viscous vehicle from dry materials and this is possible because of the fluid nature of the carrier. See column 3, lines 10-20. The viscous liquid of Roorda et al. includes aqueous solution, non-aqueous solution and undiluted non-aqueous liquids (column 3, lines 50-55). The viscous vehicle of Roorda et al. includes comprises polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol (column 4, lines 5-15), polylactic/glycolic acid, PLGA (column 9, example 1), and polyalcohols such as sorbitol (column 6, lines 30-31). Roorda et al. suggests that one can control the rate of release of the biologically effective agent by varying the size of the particles, and this affords one to achieve a desired release rate for a particular application (column 3, lines 32-35). Therefore, one can select the size of the particle that will result in the desired release rate, be it for over a period of two or more

days (column 3, lines 35-40). The concentration of the polymer affects the viscosity of the vehicle such that a polymer concentration is selected to achieve the desired viscosity (column 4, lines 24-34). Roorda et al. recommends the viscosity of the vehicle to range from about 10 to about 2,000,00 centipoise, cautions that the viscosity will be different for different applications and polymer and particle concentration affect the viscosity (column 4, lines 41-64). Roorda et al. further teaches that the biologically effective agent comprises from about 1-60% of the weight of the particles (column 6, lines 49-51), and the biologically effective agents are antibacterial, antiviral, anti-inflammatory and tissue regeneration agents, and local anesthetics (column 5, lines 33-44).

3. The Examiner's Rationale for the Obviousness Rejection Based on the '687 Patent

In the first office action the Examiner explained the rejection based on the '687 patent (Nuwayser) by stating:

> Nuwayser discloses a sustained release transdermal composition having a zero order release of drugs to designated skin are of the user (title and abstract). The drug material of Nuwayser comprises antibodies, antibacterial agents, hormones, and steroids (column 10, lines 23-30). Nuwayser teaches a viscous delivery vehicle (column 5, line 28) comprising of biodegradable polylactide polymer (column 10, lines 20-23) and glycerol for zero order release of drug microparticles uniformly dispersed and suspended in the viscous liquid (claims 1-10).

4. The Examiner's Rationale for the Obviousness Rejection Based on a Combination of the '250 Publication, the '912 Patent and the '687 Patent

In the first office action the Examiner explained the rejection based on a combination of the '250 publication (Knepp et al.), the '912 patent (Roorda et al.), and the '687 patent (Nuwayser) by stating:

> Knepp et al. is silent on the viscosity of the vehicles in which the flowable powder formulation of proteins, hormones and peptides. Nuwayser teaches viscous delivery vehicle comprising of biodegradable polymer for the sustained release of uniformly dispersed and suspended microparticles of hormones, steroids

and antibacterial agents. Roorda et al. teaches that the viscosity of the vehicle is controlled by the concentration of the polymer and biologically effective particles. Roorda et al. also teaches that the particle size influences the release rate of the particles from the vehicle. Roorda et al. suggests that one can select a particle size to achieve a desired release rate, and polymer and particle concentration for the desired vehicle viscosity. See the preceding paragraphs for the discussions.

The expected result is a non-aqueous uniform bio-compatible viscous delivery vehicle for suspending and delivering beneficial agents at a release rate that is determined by the choice of particle size. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the teachings of Knepp et al. and Roorda et al. in the manner taught by Nuwayser. One having ordinary skill in this art would have been motivated to select polymer and polymer concentration to build a non-aqueous homogeneous bio-compatible viscous delivery vehicle that has the required viscosity for the desired application, and choose a stable flowable biologically effective agent having the appropriate particle size for suspension and delivery from the viscous vehicle. The burden is on the applicant to demonstrate the criticality of the slow flow rate and the exit shear rate of 1×10^{-7} reciprocal second. Knepp et al. (page 14, lines 11) teaches that it is normal practice to include ascorbic acid, anti-oxidant in dilute aqueous peptide and protein formulations and also that formulation of dry protein or nucleic acid powders is well known in the art (page 17, line 30). It is therefore prima facie obvious to include anti-oxidant in the formulation.

In the second office action the Examiner explained the rejection based on a combination of the '250 publication (Knepp et al.), the '912 patent (Roorda et al.), and the '687 patent (Nuwayser) by stating:

Knepp et al. discloses a delivery vehicle comprising proteins, peptides, hormones, non-ionic surfactants, sucrose, raffinose, sorbitol, dextran, buffers and mineral oil. Nuwayser teaches a viscous delivery vehicle comprising biodegradable polymer, glycerol, and microparticles of hormones, steroids and antibacterial agents. Roorda et al. teaches viscous delivery vehicle comprising sorbitol, anti-bacterial agents, antiviral, anti-inflammatory and tissue regeneration agents, polyvinylpyrrolidone

and polylactic/glycolic acid. Nuwayser and Roorda et al. teach viscous delivery vehicles comprising antibacterial agents and Nuwayser's vehicle in addition comprises hormones and steroids. Knepp et al. teaches a delivery vehicle comprising peptides, proteins, hormones and steroids. The suggestion or motivation stems from the fact that all three references teach delivery vehicles comprising antibacterial agents (Roorda and Nuwayser) and hormones and steroids (Nuwayser and Knepp et al). Thus there is reasonable expectation of success for a delivery vehicle comprising sorbitol, anti-bacterial agents, antiviral, anti-inflammatory and tissue regeneration agents, polyvinylpyrrolidone and polylactic/glycolic acid, proteins, peptides, hormones, non-ionic surfactants, sucrose, raffinose, sorbitol, dextran, buffers, mineral oil, biodegradable polymer, glycerol, and microparticles of hormones and steroids.

Examiner disagrees with applicants that Roorda et al. teaches away from the polymer coated active agent of Nuwayser. In the section cited by the applicant, that is column 2, lines 15-21, Roorda et al. points out one of the solutions offered to improve the teachings of the prior and further states the difficulty associated with that solution. Specifically, Roorda et al. teaches that the particle size influences the release rate of the particles from the vehicle and suggests that one can select a particle size to achieve a desired release rate, and polymer and particle concentration for the desired vehicle viscosity. See paper number 4.

The expected result from combining the teachings of the cited references on record is a non-aqueous uniform bio-compatible viscous delivery vehicle for suspending and delivering beneficial agents at a release rate that is determined by the choice of particle size.

Therefore, it is the position of the examiner that the instant invention is obvious over the cited references of record. Knepp et al. (page 14, lines 11) teaches that it is normal practice to include ascorbic acid, anti-oxidant in dilute aqueous peptide and protein formulations and also that formulation of dry protein or nucleic acid powders is well known in the art (page 17, line 30). It is therefore prima facie obvious to include anti-oxidant in the formulation.

In the Advisory Action a two line explanation is given about the claims

The amendments do not place the claims in condition for allowance. The scope of the claims broadly read on the prior art which teaches the generic concept of two carrier vehicles/system.

X. ARGUMENT

A. The Claims Are Not Rendered Obvious by a Combination of the '250 Publication and the '912 Patent in View of the '687 Patent

Claims 1-33 and 35-38 stand rejected under 35 U.S.C. §103(a) as being obvious over Knepp et al. and Roorda et al. in view of Nuwayser. As set forth in the final office action of December 28, 2000, the Examiner states that Knepp et al. discloses a delivery vehicle comprising proteins, peptides, hormones, non-ionic surfactants, sucrose, raffinose, sorbitol, dextran, buffers and mineral oil. The Examiner cites Nuwayser as teaching a viscous delivery vehicle comprising biodegradable polymer, glycerol, and microparticles of hormones, steroids and antibacterial agents. Roorda et al. was cited as teaching a viscous delivery vehicle comprising sorbitol, anti-bacterial agents, antiviral, anti-inflammatory and tissue regeneration agents, polyvinylpyrrolidone and polylactic/glycolic acid. Applicants respectfully traverse this rejection.

In the Advisory Action of April 27, 2001, the rejection stated that the claims broadly read on the prior art which teaches the generic concept of two carrier vehicles/system. Applicants respectfully traverse this rejection and point out that three component non-aqueous single phase viscous vehicles were not addressed in the office actions or Advisory Action.

Applicants respectfully point out that the claims pending in this application deal with two and/or three component single phase non-aqueous viscous vehicles that are capable of suspending and uniformly dispensing at least one beneficial agent; formulations in which a beneficial agent is uniformly suspended

in the vehicle; methods of preparing the vehicle or the formulation; and methods of treatment.

Knepp et al. is directed to formulations in which an active agent is suspended in one anhydrous, hydrophobic, aprotic, non-polar vehicle of low reactivity. The vehicle is listed in Knepp et al. as including mineral oil, perfluorodecalin, methoxyflurane, perfluorotributylamine and tetradecane. Active agents in Knepp et al. are prepared for formulation with a vehicle by adding protective agents to the active agent during processing.

Roorda et al. is directed to aqueous formulations in which the active agent is mixed with a polymeric binder to form a matrix that retains the biologically active agent. The examples of Roorda et al. teach preparation of pellets of active agent mixed with a polymeric binder and then suspended in an aqueous sodium carboxymethylcellulose solution.

The Examiner combined Knepp et al. and Roorda et al. based on the preparation of formulations including an active agent. Knepp et al. was stated as being silent on the viscosity of the vehicles but teaching flowable powder formulations of proteins, hormones and peptides. Roorda et al. was stated as teaching the viscosity of the vehicle controlled by the concentration of the polymer and biologically effective particles. Nuwayser was stated as teaching viscous delivery vehicle comprising biodegradable polymer for the sustained release of uniformly dispersed and suspended microparticles of hormones,

Some of the claims on appeal teach non-aqueous single phase viscous vehicles prepared using 2 components. Some of the claims on appeal teach non-aqueous single phase viscous vehicles prepared using 3 components. Some of the claims on appeal teach formulations of active agent uniformly suspended in a non-aqueous single phase viscous vehicle. Applicant respectfully points out that the components of the non-aqueous single phase viscous vehicle should not be confused with a formulation comprising an active agent suspended in such a vehicle.

Applicants respectfully point out that Knepp et al. teaches a single component vehicle and an active agent that may be in the form of a proteinaceous powder with excipients added to the powder. Roorda teaches aqueous solutions in which the active agent is in a matrix with a polymeric binder and the vehicle is aqueous. Nuwayser teaches a transdermal formulation in which the active agent is incorporated in polymeric microparticles and suspended in a single base.

In order for the Examiner to meet the burden of establishing a *prima facie* case of obviousness, there must be some reason, suggestion, or motivation found in the prior art which would lead a person of ordinary skill in the field of the invention to make a combination of prior art, In re Oetiker, 24 USPQ2d 1443 (Fed. Cir. 1992). This decision also cautions that the required knowledge cannot come from applicants' invention itself. In those instances where the prior art gives general guidelines without being specific as to the particular form of the claimed invention and how to achieve it, it has been held that such a situation is one of "obvious to try" which does not make the invention obvious under 35 U.S.C. §103. (See Ex parte Obukowicz, 27 USPQ2d 1065 (BPAI 1993).

The prior art must be looked at as a whole at the time the invention was made (W.L. Gore & Associates v. Garlock, Inc. 220 USPQ 303, 313 (Fed. Cir. 1983) cert. Denied 469 U.S. 851 (1984).

As discussed above, the '250 publication (Knepp et al.) relates to protein formulations containing one vehicle. All of the examples teach one component vehicles. On page 9, lines 14-21, it is again stated that "an anhydrous, hydrophobic, aprotic non-polar vehicle" is used. The Examiner has referred to Knepp et al. as disclosing formulations containing vehicles (plural, not singular). The Examiner has also combined any components of the formulation that are mixed with the active agent prior to adding the single component vehicle as part of the vehicle.

Applicants respectfully point out that the subject invention is directed to vehicles in which the components form a non-aqueous single phase viscous

vehicle. The non-aqueous single phase viscous vehicle is then mixed with the active agent such that the active agent is uniformly suspended in the non-aqueous single phase viscous vehicle.

As discussed above, the '912 patent (Roorda et al.) relates to aqueous formulations in which the active agent is mixed with a polymeric binder to form microparticles. The microparticles are then mixed with an aqueous solvent. Although the '912 patent mentions that the liquids can be aqueous, non-aqueous, or undiluted non-aqueous liquids, all of the examples teach aqueous formulations.

Applicants respectfully point out that the subject invention is directed to non-aqueous single phase viscous vehicles prepared using at least 2 or 3 components. The non-aqueous single phase viscous vehicle is then mixed with the active agent such that the active agent is uniformly suspended in the non-aqueous single phase viscous vehicle.

As discussed above, the '687 patent (Nuwayser) relates to transdermal formulations in which the active agent is incorporated in polymer microparticles, then ground and coated with a film-forming polymer. This coated particle is then suspended in a base such as Vaseline.

Applicants respectfully point out that the subject invention is directed to non-aqueous single phase viscous vehicles that are prepared from at least 2 or 3 components. The non-aqueous single phase viscous vehicle is then mixed with the active agent such that the active agent is uniformly suspended in the non-aqueous single phase viscous vehicle.

The Examiner's reliance on a combination of these 3 pieces of art is suspect. The portions of these 3 pieces of art that have been pointed out teach active ingredients that are combined with other ingredients prior to formulation with a vehicle. In addition, in the Advisory Action dated April 27, 2001, the rejection discussed only two carrier vehicles. The claims of the subject invention also teach 3 component non-aqueous single phase viscous vehicles.

The combination of art starts with a combination of the '250 publication and the '912 patent and then relies on the teachings in the '687 patent. Applicant submits that this combination of documents undoubtedly violates the caveat set forth in In re Fritch, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) where the court stated: "It is impermissible to use the claimed invention as an instruction manual or *template* to piece together the teachings of the prior art so that the claimed invention is rendered obvious." The '250 publication does not teach two or three component non-aqueous single phase viscous vehicles. The '912 and '687 patents teach preparing polymer matrices or microparticles with the active agent then suspending the protected agent in a vehicle or base.

Those of ordinary skill in the art would certainly not arrive at the presently claimed invention from the collective teachings of the 3 cited references. Even if valid reasons exist for concentrating on the passages referred to by the Examiner one would still not arrive at the presently claimed invention.

The rejection based on the combination of the 3 cited references further demonstrates the selective reliance on isolated teachings of the patents without regard to the substantial reasons that would counsel away from making the combination.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to be so found either in the references

themselves or in the knowledge generally available to one of ordinary skill in the art. In re Fine, 5 USPQ2d 1596 (Fed. Cir. 1988; In re Jones, 21 USPQ2d 1941 (Fed. Cir. 1992).

Applicants respectfully point out that there must be some motivation to combine the '250 publication and the '912 patent in view of the '687 patent. However, non of these references suggest a single phase non-aqueous viscous vehicle prepared using at least 2 or 3 components, or a formulation prepared using such a single phase non-aqueous viscous vehicle.

Applicants respectfully further point out that the references must present a reasonable expectation of success. There is no such reasonable expectation of success in the references cited. Knepp et al. uses a single component vehicle. Roorda et al. uses a protective coating on the active protein prior to adding a solvent. Nuwayser prepared protected proteins in microparticles or microspheres. None of these references even hint at the success of a non-aqueous single phase viscous vehicle.

Applicants also respectfully point out that the 3 references do not teach all of the claim limitations of the presently claimed invention. None of these references teach a non-aqueous single phase viscous vehicle that is prepared from at least 2 or 3 components. If the 3 references do not teach the presently claimed vehicles, then they do not teach the presently claimed formulations using such vehicles. The Examiner has also not discussed the claims directed to methods of preparing either the vehicles or the formulations using the vehicles. The only discussion related to the method of treatment claims in the office actions is a statement that claim 34 is objected to for depending from a rejected claim.

For these reasons Applicants respectfully submit that the 3 references cited do not form the basis for a *prima facie* case of obviousness. For the above reasons, Applicants believe that claims 1-38 are not obvious in light of the '250 publication and the '912 patent in view of the '687 patent.

XI. CONCLUSIONS

For the reasons set forth above, appellants respectfully submit that the claims are not rendered obvious by the cited patents. Accordingly, Appellants respectfully request reversal of each of the rejections on appeal.

Respectfully submitted,

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APPENDIX A

Claims

1. A stable non-aqueous single phase biocompatable viscous vehicle capable of suspending beneficial agents and homogeneously dispensing said beneficial agent over an extended period of time at body temperature and at low flow rates.

2. The vehicle of claim 1 comprising two components selected from the group consisting of solvent, surfactant, and polymer, wherein the two components are not of the same type.

3. The vehicle of claim 1 comprising at least two components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type.

4. The vehicle of claim 1 which comprises three components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type.

5. The vehicle of claim 2 or 4 wherein said solvent is selected from the group carboxylic acid esters, polyhydric alcohols, polymers of polyhydric alcohols, fatty acids, oils, propylene carbonate, lauryl alcohol, and esters of polyhydric alcohols.

6. The vehicle of claim 2 or 4 wherein said surfactant is selected from the group esters of polyhydric alcohols, ethoxylated castor oil, polysorbates, esters or ethers of saturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers.

7. The vehicle of claim 2 or 4 wherein said polymer is selected from the group polyesters, pyrrolidones, esters or ethers of unsaturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers.

8. The vehicle of claim 2 wherein the ratios of the components are in the range of 40:60 to 60:40.

9. The vehicle of claim 4 wherein the ratios of the components are in the range of about 30% to about 50% for solvent, about 5% to about 20% for surfactant, and about 5% to about 60% for polymer.

10. The vehicle of claim 4 wherein the polymer is polyvinlypyrrolidone, the surfactant is gml, and the solvent is lauryl lactate.

11. The vehicle of claim 4 wherein the polymer is polyvinlypyrrolidone, the surfactant is polysorbate, and the solvent is lauryl lactate.

12. The vehicle of claim 1 which comprises an antioxidant.

13. The vehicle of claim 12 wherein said antioxidant is selected from the group consisting of tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate.

14. A stable non-aqueous viscous protein formulation comprising

a) at least one beneficial agent, and

b) a non-aqueous single phase biocompatible viscous vehicle, which formulation is capable of being uniformly dispensed over an extended period of time at a low flow rate.

15. A non-aqueous formulation comprising at least one beneficial agent uniformly suspended in a non-aqueous single phase biocompatible viscous vehicle, which formulation can be delivered from an implantable drug delivery system such that the exit shear rate of the formulation is between about 1 and 1×10^{-7} reciprocal second.

16. The formulation of claim 14 wherein said formulation is stable at body temperature for extended periods of time.

17. The formulation of claim 14 which comprises at least about 0.1% (w/w) beneficial agent.

18. The formulation of claim 14 which comprises at least about 10% (w/w) beneficial agent.

19. The formulation of claim 14 wherein said beneficial agent is selected from the group consisting of peptide, protein, nucleotide, hormone, virus, or antibody.

20. The formulation of claim 19 wherein said beneficial agent is a protein.

21. The formulation of claim 14 which is stable at 65° C for at least about 2 months.

22. The formulation of claim 14 which is stable at 37° C for at least about 3 months.

23. The formulation of claim 14 which is stable at 37° C for at least about one year.

24. The formulation of claim 14 which is adapted for use in an implantable drug delivery device.

25. The formulation of claim 14 wherein said vehicle is selected from the group consisting of solvent, surfactant and polymer.

26. The formulation of claim 14 wherein said vehicle comprises an antioxidant.

27. The formulation of claim 14 comprising a beneficial agent which has been dried to a low moisture content prior to incorporation in said formulation.

28. The formulation of claim 14 which is stable after sterilization.

29. A method for preparing the stable single phase viscous vehicle of claim 1 comprising the steps of (1) blending the ingredients at elevated temperature under dry conditions to allow them to liquify, and (2) allowing the liquid from step (1) to cool to room temperature.

30. A method for preparing the stable formulation of claim 14 comprising combining the single phase viscous vehicle and beneficial agent under dry conditions and blending them under vacuum at elevated temperature to uniformly disperse the beneficial agent in the vehicle, and allowing the formulation to cool to room temperature.

31. The method of claim 30 wherein at least about 0.1% (w/w) beneficial agent is suspended in said vehicle.

32. The method of claim 30 wherein at least about 10% (w/w) beneficial agent is suspended in said vehicle.

33. A method for treating a subject suffering from a condition which may be alleviated by administration of a beneficial agent comprising administering to said subject a therapeutically effective amount of the formulation of Claim 14.

34. The method of claim 33 wherein said administration is parenteral administration.

35. The method of claim 33 wherein said administration is long-term continuous administration.

36. The method of claim 33 wherein said administration is accomplished by use of an implantable drug delivery system.

37. The method of claim 33 wherein said daily administration continues for a period selected from the group consisting of about 3 months, about 6 months, and about 12 months.

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38. The method of claim 37 wherein said daily administration is accomplished using an implantable drug delivery system.

APPENDIX B

Claims:

1. A stable non-aqueous single phase biocompatable viscous vehicle comprising two components selected from the group consisting of solvent, surfactant, and polymer, wherein the two components are not of the same type, said vehicle being capable of suspending beneficial agents and homogeneously dispensing said beneficial agent over an extended period of time at body temperature and at low flow rates.

3. A stable non-aqueous single phase biocompatable viscous vehicle comprising at least two components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, said vehicle being capable of suspending beneficial agents and homogeneously dispensing said beneficial agent over an extended period of time at body temperature and at low flow rates.

4. A stable non-aqueous single phase biocompatable viscous vehicle which comprises three components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, said vehicle being capable of suspending beneficial agents and homogeneously dispensing said beneficial agent over an extended period of time at body temperature and at low flow rates.

5. The vehicle of claim 1, 3 or 4 wherein said solvent is selected from the group carboxylic acid esters, polyhydric alcohols, polymers of polyhydric alcohols, fatty acids, oils, propylene carbonate, lauryl alcohol, and esters of polyhydric alcohols.

6. The vehicle of claim 1, 3, or 4 wherein said surfactant is selected from the group esters of polyhydric alcohols, ethoxylated castor oil, polysorbates, esters

or ethers of saturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers.

7. The vehicle of claim 1, 3, or 4 wherein said polymer is selected from the group polyesters, pyrrolidones, esters or ethers of unsaturated alcohols, and polyoxyethylenepolyoxypropylene block copolymers.

8. The vehicle of claim 1 wherein the ratios of the components are in the range of 40:60 to 60:40.

9. The vehicle of claim 4 wherein the ratios of the components are in the range of about 30% to about 50% for solvent, about 5% to about 20% for surfactant, and about 5% to about 60% for polymer.

10. The vehicle of claim 4 wherein the polymer is polyvinlypyrrolidone, the surfactant is gml, and the solvent is lauryl lactate.

11. The vehicle of claim 4 wherein the polymer is polyvinlypyrrolidone, the surfactant is polysorbate, and the solvent is lauryl lactate.

12. The vehicle of claim 1, 3, or 4 which comprises an antioxidant.

13. The vehicle of claim 12 wherein said antioxidant is selected from the group consisting of tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate.

14. A stable non-aqueous viscous protein formulation comprising

a) at least one beneficial agent, and

b) a non-aqueous single phase biocompatible viscous vehicle comprising two components selected from the group consisting of solvent, surfactant, and polymer, wherein the two components are not of the same type, which

formulation is capable of being uniformly dispensed over an extended period of time at a low flow rate.

15. A non-aqueous formulation comprising at least one beneficial agent uniformly suspended in a non-aqueous single phase biocompatible viscous vehicle comprising two components selected from the group consisting of solvent, surfactant, and polymer, wherein the two components are not of the same type, which formulation can be delivered from an implantable drug delivery system such that the exit shear rate of the formulation is between about 1 and 1 x 10^{-7} reciprocal second.

16. The formulation of claim 14 wherein said formulation is stable at body temperature for extended periods of time.

17. The formulation of claim 14 which comprises at least about 0.1% (w/w) beneficial agent.

18. The formulation of claim 14 which comprises at least about 10% (w/w) beneficial agent.

19. The formulation of claim 14 wherein said beneficial agent is selected from the group consisting of peptide, protein, nucleotide, hormone, virus, or antibody.

20. The formulation of claim 19 wherein said beneficial agent is a protein.

21. The formulation of claim 14 which is stable at 65° C for at least about 2 months.

22. The formulation of claim 14 which is stable at 37° C for at least about 3 months.

23. The formulation of claim 14 which is stable at 37° C for at least about one year.

24. The formulation of claim 14 which is adapted for use in an implantable drug delivery device.

25. The formulation of claim 14 wherein said vehicle is selected from the group consisting of solvent, surfactant and polymer.

26. The formulation of claim 14 wherein said vehicle comprises an antioxidant.

27. The formulation of claim 14 comprising a beneficial agent which has been dried to a low moisture content prior to incorporation in said formulation.

28. The formulation of claim 14 which is stable after sterilization.

29. A method for preparing the stable single phase viscous vehicle of claim 1, 3, or 4 comprising the steps of (1) blending the ingredients at elevated temperature under dry conditions to allow them to liquify, and (2) allowing the liquid from step (1) to cool to room temperature.

30. A method for preparing the stable formulation of claim 14, 41, or 42 comprising combining the single phase viscous vehicle and beneficial agent under dry conditions and blending them under vacuum at elevated temperature to uniformly disperse the beneficial agent in the vehicle, and allowing the formulation to cool to room temperature.

31. The method of claim 30 wherein at least about 0.1% (w/w) beneficial agent is suspended in said vehicle.

32. The method of claim 30 wherein at least about 10% (w/w) beneficial agent is suspended in said vehicle.

33. A method for treating a subject suffering from a condition which may be alleviated by administration of a beneficial agent comprising administering to said subject a therapeutically effective amount of the formulation of Claim 14.

34. The method of claim 33 wherein said administration is parenteral administration.

35. The method of claim 33 wherein said administration is long-term continuous administration.

36. The method of claim 33 wherein said administration is accomplished by use of an implantable drug delivery system.

37. The method of claim 33 wherein said daily administration continues for a period selected from the group consisting of about 3 months, about 6 months, and about 12 months.

38. The method of claim 37 wherein said daily administration is accomplished using an implantable drug delivery system.

39. A stable non-aqueous viscous protein formulation comprising

a) at least one beneficial agent, and

b) a non-aqueous single phase biocompatible viscous vehicle comprising at least two components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type , wherein the components are not of the same type, which formulation is capable of being uniformly dispensed over an extended period of time at a low flow rate.

40. A stable non-aqueous viscous protein formulation comprising

a) at least one beneficial agent, and

b) a non-aqueous single phase biocompatible viscous vehicle which comprises three components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, which formulation is capable of being uniformly dispensed over an extended period of time at a low flow rate.

41. A non-aqueous formulation comprising at least one beneficial agent uniformly suspended in a non-aqueous single phase biocompatible viscous vehicle comprising at least two components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, which formulation can be delivered from an implantable drug delivery system such that the exit shear rate of the formulation is between about 1 and 1 x 10^{-7} reciprocal second.

42. A non-aqueous formulation comprising at least one beneficial agent uniformly suspended in a non-aqueous single phase biocompatible viscous vehicle which comprises three components selected from the group consisting of solvent, surfactant, and polymer, wherein the components are not of the same type, which formulation can be delivered from an implantable drug delivery system such that the exit shear rate of the formulation is between about 1 and 1 x 10^{-7} reciprocal second.

06-27-01

Practitioner's Docket No. ARC 2914R1

PATENT

13/Reg Ext of time (1 mo)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Berry, Stephen A.; Fereira, Pamela J.; Dehnad, Houdin; and Muchnik, Anna

Application No.: 09/497,422 Group No.: 1615
Filed: 02/03/2000 Examiner: B. Fubara
For: Stable Non-Aqueous Single Phase Viscous Vehicles and Formulations Utilizing Such Vehicles

Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF APPEAL BRIEF (PATENT APPLICATION--37 C.F.R. 1.192)

1. Transmitted herewith, in triplicate, is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed on June 25, 2001.

2. STATUS OF APPLICANT

This application is on behalf of other than a small entity.

3. FEE FOR FILING APPEAL BRIEF

Pursuant to 37 C.F.R. 1.17(c), the fee for filing the Appeal Brief is:

CERTIFICATE OF MAILING/TRANSMISSION (37 C.F.R. 1.8(a))

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

☒ deposited with the United States Postal Service with sufficient postage as Express mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Express Mail No.: EL523935265US

Date: June 26, 2001

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☐ transmitted by facsimile to the Patent and Trademark Office.

Katrina M. Ghafghaichi
Signature

Katrina M. Ghafghaichi
(*type or print name of person certifying*)

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01 FC:115 110.00 CH

Other than a small entity	$310.00
Appeal Brief fee due	$ 310.00

4. EXTENSION OF TERM

The proceedings herein are for a patent application and the provisions of 37 C.F.R.section 1.136 apply.

Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

5. TOTAL FEE DUE

The total fee due is:

Appeal brief fee	$ 310.00
Extension fee (if any)	$
TOTAL FEE DUE	**$ 310.00**

6. FEE PAYMENT

Charge Account No. 01-1173 the sum of $310.00

A duplicate of this transmittal is attached.

7. FEE DEFICIENCY

If any additional extension and/or fee is required, this is a request therefor to charge Account No. 01-1173.

Date: June 26, 2001

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